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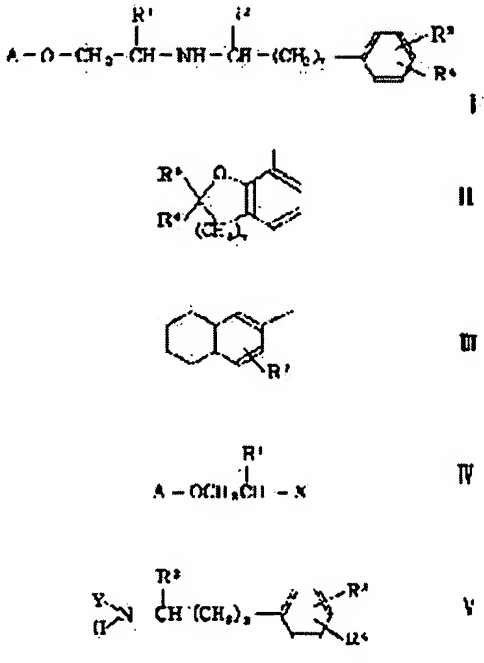
(54) NEW ARYLOXYALKYLAMINE DERIVATIVE OR ITS SALT

(57)Abstract:

PURPOSE: To provide a new aryloxyalkylamine derivative having remarkably excellent selective affinity to 5-HT1A receptor and useful as a treating agent for symptoms relating to central neruous system such as anxiety, depression, disorder of memory, etc.

CONSTITUTION: The aryloxyalkylamine derivative of formula I [(A is group of formula II or formula III); R1, R2, R5 and R6 are H or lower alkyl; R3 and R4 are H, lower alkyl, lower alkoxy, lower alkylthio or OH (R" and R' are not H at the same time); R7 is lower alkoxy; (n) is 1-5; (m) is 1-4] or its salt, e.g. N-[2-(8-chromanyloxy) ethyl]-p-methoxyphenetylamine. The compound of formula I can be produced e.g. by reacting a compound of formula IV (X is eliminable group such as halogen or methylsulfonyloxy) with a compound of formula V (Y is H or protecting group such as benzyl) and optionally removing the protecting group.



LEGAL STATUS

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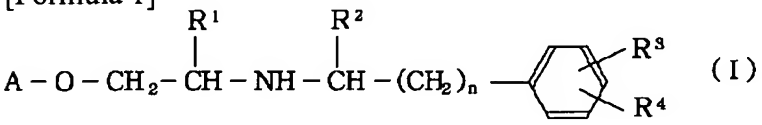
CLAIMS

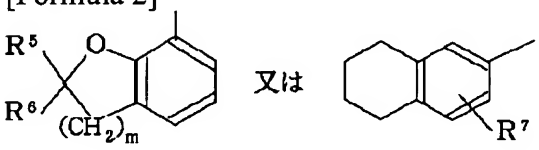
[Claim(s)]
[Claim 1] The new aryloxy alkylamine derivative shown by the following general formula (I), or its salt.

[Formula 1]



(I)

(The inside of a formula and A are the following general formula (II).)
[Formula 2]



(II)

In the radical come out of and shown, R1, R2, R5, and R6 are the same. or it differs and R3 and R4 are the same in a hydrogen atom or a low-grade alkyl group -- or -- differing -- a hydrogen atom, a low-grade alkyl group, a lower alkoxy group, a low-grade alkylthio group, or a hydroxy group (however, the case where both R3 and R4 are hydrogen atoms is removed.) n means a lower alkoxy group and, as for the integer of 1-5, and m, R7 means the integer of 1-4, respectively.
[Claim 2] N-[2-(8-chromanyl oxy-) ethyl]-p-methoxy phenethylamine or its acid addition salt [claim 3] An N-[2-(8-chromanyl oxy-) ethyl]-4-(p-methoxypheny) butylamine or its acid addition salt [claim 4] p-methoxy-N-[2-(1-methoxy - 5, 6, 7, 8-tetrahydro-2-naphthyloxy) ethyl] phenethylamine or its acid addition salt

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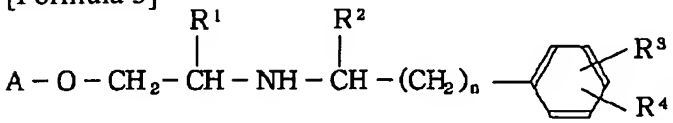
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] Physic and since it has alternative compatibility to a 5-HT1A acceptor especially, this invention relates to a new aryloxy alkylamine derivative useful as a therapy agent of the condition of disease in which central nervous systems, such as anxiety and a memory disorder to shoot, participate, or its salt.
[0002]
[Description of the Prior Art] [by which it has been shown clearly that neurotransmitter serotonine (5-hydroxytryptamine: write it as 5-HT hereafter.) is connected with appetite, storage, thermoregulation, sleep, a sexual act, anxiety, depression, and many physiological phenomena including hallucination action directly or indirectly in several years recently -- prodigal -- non -- (30 Glenon, R.A., J.Med.Chem. 1 (1987))].
[0003] It is recognized that two or more types exist in a 5-HT acceptor. These acceptors are classified as 5-HT1, 5-HT2, and 5-HT3 acceptor, and first 5-HT1 is further classified into 5-HT1A, 5-HT1B, 5-HT1C, and 5-HT1D as a subclass. It is thought that it is effective in the therapy or prevention of various illnesses in which, as for a 5-HT1A acceptor, anxiety participates, and, as for the compound which is considered to participate in the illness of a central nervous system, such as striking, therefore has compatibility to a 5HT1A acceptor, a central nervous system participates in the subclass of above-mentioned 5-HT1.
[0004] as the typical thing of a compound which has alternative compatibility to a 5-HT1A acceptor conventionally -- buspirone (Buspirone; compound given in the Merck index 11st edition 229 pages), and BINOSU pyrone (M.Hibert et al. and Br.J.Pharmacol, 1988, 93, compound indicated by 2 pages as an example 9 at JP,61-246180,A as MDL73005EF) etc. -- it is known. It is thought that such a compound may serve as remedies, such as a failure of the failure of the anxiety, schizophrenia, and diet intake which strike, study, and recognition, an Alzheimer disease or hypertension, and ******, and Kamiichi of the buspirone has already been carried out as an anti-anxiety drug especially.
[0005]
[Problem(s) to be Solved by the Invention] as a result of repeating the research on a 5-HT1A acceptor, inventing various compounds and having advanced screening, this invention person etc. does the knowledge of having the alternative compatibility which was markedly alike to the 5-HT1A acceptor, and was excellent, and came to complete this invention. [of the new aryloxy alkylamine derivative]
[0006] In addition, although the aryloxy alkylamine derivative is reported to the Patent Publication Heisei No. 501393 [one to] official report, the compound of this invention is a new molecular entity which differs in the class of substituent in an aryloxy group. Moreover, this official report only explains the operation as a fungicide, and has not indicated the compatibility over a 5-HT acceptor at all.
[0007]
[Means for Solving the Problem] That is, this invention offers the new aryloxy alkylamine derivative shown by the following general formula (I), or its salt permitted pharmaceutically.

[0008]
[Formula 3]



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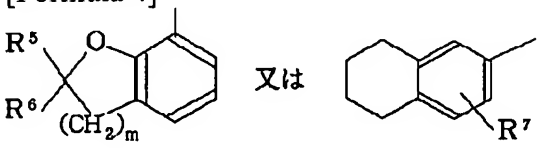

(II)

[0011] it comes out and R1, R2, R5, and R6 are the same in the radical shown -- or it differs and R3 and R4 are the same in a hydrogen atom or a low-grade alkyl group -- or it differs, and n means a lower alkoxy group and, as for the integer of 1-5, and m, R7 means the integer of 1-4 for a hydrogen atom, a low-grade alkyl group, a lower alkoxy group, a low-grade alkylthio group, or a hydroxy group (however, R3 and R4 remove the case where it is a hydrogen atom.), respectively.
[0012] It explains in full detail per this invention compound below. The word "low-grade" Becoming means the hydrocarbon chain of the shape of the shape of a straight chain of 1-6 carbon numbers, and branching among this specification. therefore, as a "low-grade alkyl group"

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TECHNICAL FIELD

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PRIOR ART

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EFFECT OF THE INVENTION

[Effect of the Invention]
[0028] The compound of this invention has and divides compatibility to a 5-HT acceptor, and shows very high compatibility to the 5-HT1A acceptor which is the subtype of a 5-HT acceptor. for this reason, the compound of this invention -- 5-HT -- it can use for the treatment of the various diseases in which a nervous system participates. As such a disease, the failure of moral nervous disease [, such as anxiety, stress and schizophrenia to shoot,], sexual functional disorder, and diet intake, a somnipathy, motion sickness, drug dependence, etc. are raised. Furthermore, these can be used for treatment, such as cerebral apoplexy, brain ischemia, dysgnosia, study and a memory disorder, and an Alzheimer disease. These can be used to the failure of the circulatory system, such as ****** and hypertension, further again. Since some compounds which this invention furthermore includes have compatibility in an adrenergic alpha receptor, the compound concerned can be used as the therapy agent and cerebral circulation improvement agent of dysuria and hypertension. About the compatibility and the uneasy remission operation over the 5-HT1A acceptor of this invention compound, the example of an experiment is thing mentioned above [an example] and explained below.
[0029] [The example 1 of an experiment]
The compatibility over compatibility 1 experiment approach 5-HT1A to a 5-HT1A acceptor is Peroutka. It asked by measuring the permutation of 8-OH-DPAT which carried out tritium labeling using the sample of a rat hippocampus according to an approach (J.Neurochem.47,529 (1986)), and expressed as a Ki value. Ki value of the aforementioned buspirone used as this invention compound and a contrast compound is shown in the following table 1.
2) Experimental result [0030]
[Table 1]

各被験化合物の５－HT_{1A}受容体に対する親和性

被験化合物	Ki値（単位：ナノモル）
ブロスピン（対照化合物）	18.5
実施例１（本発明化合物）	0.175
実施例２（本発明化合物）	0.674
実施例５（本発明化合物）	0.578
実施例１１（本発明化合物）	0.118

[0031] Consequently, the knowledge of this invention compound having remarkably powerful compatibility [as opposed to a 5-HT1A acceptor as compared with the buspirone which is a contrast compound] was carried out. for this reason, this invention compound -- 5-HT -- in the prevention or the therapy of various diseases which participates in a nervous system, it is expectable to have the more excellent effectiveness.

[0032] [The example 2 of an experiment]

The social interaction [in / for an uneasy remission operation of the uneasy remission operation 1 experiment approach this invention compound / a rat] was investigated as an index. (J.Neurosci.Methods., 2, 219 (1980)) . An uneasy remission operation is shown as an increment in social interaction time amount. The drug was injected intraperitoneally to the male Wistar rats which performed handling for several days beforehand, and it put into the cage for a trial by having made two animals into the lot after 30 minutes, and observed for 10 minutes. In the meantime, the rat measured the stinking time amount which smelled and performed active social interactions, such as action, flattery action, and action of grooming. The sum total of the number of seconds of the social interaction of for 10 minutes was searched for, and it expressed as the rate of increase (%) of the medication group to drug the group non-prescribing a medicine for the patient. this invention compound and the aforementioned buspirone as contrast -- further -- as an anti-anxiety drug -- current -- the uneasy remission operation at the time of injecting 1 mg/kg intraperitoneally, respectively is shown in Table 2 about the diazepam used widely (it is shown that front Naka and * have a significant difference at 5% or less of level of significance about the numeric value of the administration group to the group non-prescribing a medicine for the patient, and it is shown that ** has a difference same and significant at 1% or less of level of significance).

2) Experimental result [0033]

[Table 2]

表２　各被験化合物の不安寛解作用

被験化合物	社会的相互作用時間（秒）		増加率（%）
	非投与群（例数）	投与群（例数）	
ジアゼパム（対照化合物）	61.3 ± 2.9 (7)	93.7 ± 11.5** (7)	152.9
ブスピロン（対照化合物）	67.1 ± 5.7 (10)	99.9 ± 6.4 * (8)	148.9
実施例１（本発明化合物）	54.7 ± 6.0 (6)	95.0 ± 11.6* (6)	173.7
実施例12（本発明化合物）	68.1 ± 6.2 (7)	117.5 ± 9.2** (6)	172.5

[0034] Consequently, the knowledge of it being remarkable, the rate of increase of social interaction time amount being high, and the compound of examples 1 and 12 having a powerful uneasy remission operation as compared with the diazepam or buspirone which is a contrast compound, was carried out among this invention compound. For this reason, it is expectable that this invention compound has the effectiveness which was more excellent to the moral disease with various anxiety, memory disorders to shoot.

[0035] The medicine manufacture constituent which contains one sort of the compound shown by the general formula (I) or its salt or two sorts or more as an active principle is prepared using the support usually used for pharmaceutical preparation-ization, an excipient, and other additives. As the support and the excipient for pharmaceutical preparation, a solid-state, or liquid-like the matter for nontoxic physic is mentioned. As these examples, the thing of a lactose, magnesium stearate, starch, talc, gelatin, an agar, pectin, gum arabic, olive oil, sesame oil, cocoa butter, ethylene glycol, etc. and in addition to this daily use is illustrated, for example.

[0036] ****** of administration is also good with which gestalt of the parenteral administration by injections, such as internal use by a tablet, a pill, the capsule, the granule, powder, liquids and solutions, etc. or intravenous injection, and intramuscular injection, suppositories, transderma, etc.

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TECHNICAL PROBLEM

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MEANS

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[0008]
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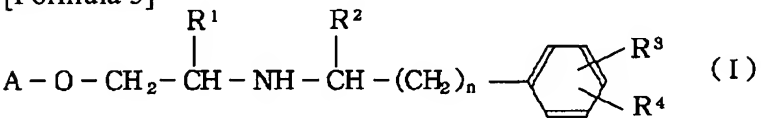

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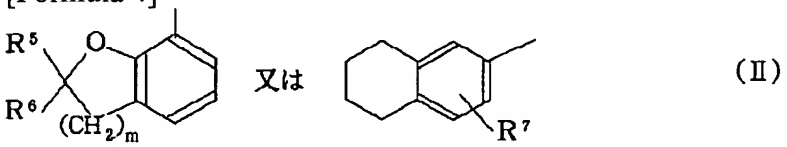

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[0012] It explains in full detail per this invention compound below. The word "low-grade" Becoming means the hydrocarbon chain of the shape of the shape of a straight chain of 1-6 carbon numbers, and branching among this specification. therefore, as a "low-grade alkyl group" For example, a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, a pentyl radical, an isopentyl radical, a neopentyl radical, a tert-pentyl radical, 1-methylbutyl radical, 2-methylbutyl radical, 1, on ** and a concrete target 2-dimethyl propyl group, hexyl group, iso hexyl group, 1-methyl pentyl radical, 2-methyl pentyl radical, 3-methyl pentyl radical, 1, and 1-dimethyl butyl, 1, 2-dimethyl butyl, 2, and 2-dimethyl butyl, 1, 3-dimethyl butyl, 2, 3-dimethyl butyl, 3, and 3-dimethyl butyl, 1-ethyl BUCHIRUKI radical, 2-ethyl butyl, 1 and 1, a 2-trimethyl propyl group, 1 and 2, a 2-trimethyl propyl group, a 1-ethyl-1-methylpropyl radical, a 1-ethyl-2-methylpropyl radical, etc. are mentioned.
[0013]

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EXAMPLE

[Example] And this invention is further explained to it at a detail. [below] [an example] In addition, the new matter is also contained in this invention raw material compound, and the process is shown in the example of reference. Moreover, what processed the process of a raw material compound and the process of this invention compound by single string is indicated according to an example.
[0038] Example of reference 18-chromanol 1.5g was dissolved in 1 and 2-dibromoethane 10ml, 10ml [of 3 convention sodium-hydroxide water solutions] and sulfuric-acid hydrogen tetrabutylammonium (TBAHS) 170mg was added, and it agitated at 70 degrees C. 1, 2-dibromoethane, and 5ml of 3 convention sodium-hydroxide water solutions were added 2 hours after, and it agitated for further 2 hours. The after [the cold] reaction mixture was extracted by dichloromethane, and the organic layer was dried with the sulfuric anhydride magnesium after washing with saturation brine. Evaporation to dryness of the solvent was carried out, and 2.6g of white crystals of 8-(2-bromoethoxy) chroman was obtained.
[0039] physicochemical -- description -- mass analysis value (EI, m/z): -- 256 (M+) and 258 (M++2)
Nuclear-magnetic-resonance spectrum (CDCl3, TMS internal standard)
delta: 4.30 (OCH2CH2B[4H, tx2, C2-H2, and] r) 1.8-2.1 (2H, m, C3-H2), 2.79 (2H, t, C4-H2) and 3.63 (2H, t, CH2Br), 4.24, 6.74 (3H, m)
The compound of the example 2 of reference and the example 3 of reference was compounded by the same approach as the example 1 of reference.
[0040] Example of reference 27-(2-bromoethoxy)-2, 3-dihydrobenzofuran [0041] physicochemical -- description -- mass analysis value (EI, m/z): -- 242 (M+) and 244 (M++2)
Nuclear-magnetic-resonance spectrum (CDCl3, TMS internal standard)
delta: 3.22 (2H, t, C3-H2), 3.62 (2H, t, CH2Br), 4.36 (2H, t, OCH2), 4.62 (2H, t, C2-H2), 6.7-6.9 (3H, m)
[0042] Example of reference 37-(2-bromoethoxy)-2, 3-dihydro - 2 and 2-dimethyl benzofuran [0043] physicochemical -- description -- mass analysis value (EI, m/z): -- 270 (M+) and 272 (M++2)
Nuclear-magnetic-resonance spectrum (CDCl3, TMS internal standard)
delta: 1.50 (6H, s, CH 3x2), 3.02 (2H, s, C3-H2), 3.62 (2H, t, CH2Br), 4.37 (2H, t, OCH2CH2Br), 6.77 (3H, m)
[0044] After mixing with example of reference 48-chromanol 700mg, acetone 7ml, monochloroacetone 520mg, 970mg of potassium carbonate, and 100mg of potassium iodide and carrying out heating reflux for 5 hours, monochloroacetone 260mg and 320mg of potassium carbonate were added, and it flowed back for further 2 hours. Acetone (8-chromanyl oxy-) 710mg was obtained by filtering out an after [the cold] solid-state, condensing filtrate, giving a column chromatography, and being eluted with the mixed solvent of hexane-ethyl acetate (85:15).
[0045] physicochemical -- description -- mass analysis value (EI, m/z): -- 206 (M+)
Nuclear-magnetic-resonance spectrum (CDCl3, TMS internal standard)
delta:1.9-2.2 (2H, m, C3' - H2), 2.28 (3H, s, CH3), 2.80 (2H, t, C4' - H2), 4.27 (2H, t, C2' - H2) and 4.56 (2H, s, COCH2O), 6.5-6.8 (3H, m)

[0046] It mixed with example of reference 5(1)8-chromanol 1.0g, acetone 10ml, chloro acene 600mg, 1.38g of potassium carbonate, and 100mg of potassium iodide, and heating reflux was carried out for 5 hours. Acetonitrile (8-chromanyl oxy-) 1.18g was obtained by filtering out an insoluble solid-state after the cold, condensing filtrate, giving a column chromatography, and being eluted with the mixed solvent of hexane-ethyl acetate (9:1).
[0047] physicochemical -- description -- mass analysis value (EI, m/z): 189 (M+)
Nuclear-magnetic-resonance spectrum (CDCl3, TMS internal standard)
delta: 1.7-1.9 (2H, m, C3' - H2), 2.55 (2H, t, C4' - H2), 4.01 (2H, t, C2' - H2) and 4.54 (2H, s, CH2CN), 6.5-6.6 (3H, m)
[0048] (2) Lithium hydride aluminum 760mg was suspended in tetrahydrofuran 10ml, and 980mg of sulfuric acids was dropped 100% under ice-cooling. After the acetonitrile (8-chromanyl oxy-) 1.16g tetrahydrofuran solution (10ml) obtained by (1) was dropped here, it stirred at the room temperature for 2 hours. After adding water to reaction mixture and suspending a reaction, the sodium-hydroxide water solution was added, and the ether extracted. The solvent after desiccation was distilled off for the organic layer with sulfuric anhydride magnesium, and colorless oil-like 2-(8-chromanyl oxy-) ethylamine 1.16g was obtained.
[0049] physicochemical -- description -- mass analysis value (EI, m/z): 193 (M+)
Nuclear-magnetic-resonance spectrum (CDCl3, TMS internal standard)
delta: 1.6 (H 2 br s, NH2), 1.8-2.1 (2H, m, C3' - H2), 2.79 (2H, t, C4' - H2) and 3.08 (2H, t, CH2N), and 4. -- 02, 4.24 (4H, tx2, C2' - H2, OCH2CH2N), and 6.6-6.8 (3H, m)
[0050] Chlorosulfuric acid was cooled at -20 degrees C example of reference 6(1) 98%, and 3.0g of N-(p-methoxy phenethyl) ethyl carbamates was added small quantity every. - Keeping at 5 degrees C or less, after 2-hour churning, water was filled with reaction mixture and ethyl acetate extracted. This organic layer was washed with water and saturation brine, and it dried with sulfuric anhydride magnesium. A solvent is distilled off and it is N-[3-(chloro sulfonyl)-4-methoxy phenethyl] ethyl carbamate of a white solid-state. 2.52g was obtained.
[0051] physicochemical -- description -- mass analysis value (EI, m/z): -- 321 (M+)
Nuclear-magnetic-resonance spectrum (CDCl3, TMS internal standard)
delta: 1.22 (3H, t, OCH2CH3) 2.82 (2H, t, NCH2CH2Ar), 3.42 (2H, m, NCH2CH2Ar), 4.04 (3H, s, OCH3), 4.10 (2H, q, OCH2CH3), 4.64 (1H, br s, NHCO), 7.04 (1H, d), 7.50 (1H, dd), 7.74 (1H, d)
[0052]